



- (51) International Patent Classification:
C12Q 1/68 (2006.01)
- (21) International Application Number:
PCT/HU2013/000101
- (22) International Filing Date:
18 October 2013 (18.10.2013)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
P1200607 19 October 2012 (19.10.2012) HU
- (71) Applicant: **EGIS PHARMACEUTICALS PUBLIC LIMITED COMPANY** [HU/HU]; Keresztúri út 30-38., 1106 Budapest (HU).
- (72) Inventors: **NAGY, László**; Simonyi u. 30/C, 4028 Debrecen (HU). **MESKÓ, Bertalan**; Krucsay Márton u. 23., 4600 Kisvárd (HU). **STEINER, László**; Hadházi u. 38., 4028 Debrecen (HU). **ZAHUCZKY, Gábor**; Veres Péter u. 33., 4241 Bocskaiakert (HU). **HOLLÓ, Zolt**; Wéber Ede park 27., 2145 Kerepes (HU).
- (74) Agent: **KOVÁRI, Zoltán**; Kovári & Partners Patent and Trademark Attorneys' LLC, Attila út 125., 1012 Budapest (HU).
- (81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM,

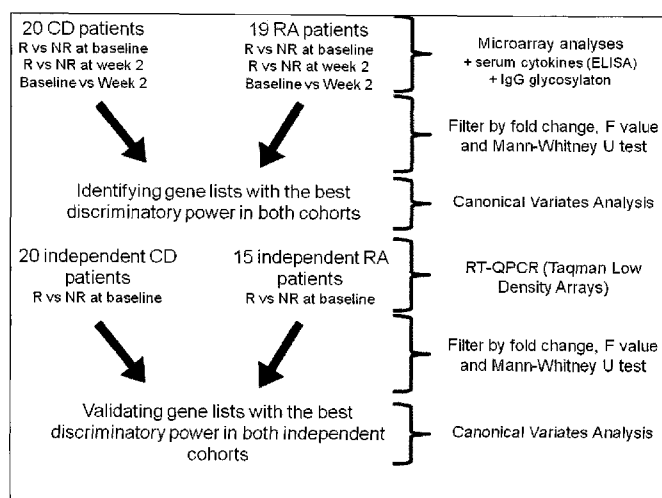
AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

- (84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

- (88) Date of publication of the international search report:
12 June 2014

(54) Title: DIAGNOSTIC METHOD FOR PREDICTING RESPONSE TO TNF α INHIBITOR**Figure 1**

- (57) Abstract: Disclosed are *in vitro* diagnostic methods for predicting whether a patient would be responsive to a treatment with a TNF α inhibitor. Said method is based on gene expression profiling. By measuring the expression profile of the disclosed genes it is possible to forecast whether a treatment by a TNF α inhibitor will be successful or not.

INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2013/000101

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/68
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 857 559 A1 (INST NAT SANTE RECH MED [FR]) 21 November 2007 (2007-11-21)	12,13
Y	claims 1-19 the whole document	1,2,7-11
X	WO 2012/061620 A1 (GENENTECH INC [US]; HOFFMANN LA ROCHE [CH]; DENNIS GLYNN JR [US]; MART) 10 May 2012 (2012-05-10)	12,13
Y	claims 1-31 the whole document	1,2,7-11
	----- -/--	

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

5 February 2014

Date of mailing of the international search report

24/04/2014

Name and mailing address of the ISA/
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Schmitt, Anja

INTERNATIONAL SEARCH REPORT

International application No

PCT/HU2013/000101

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANTONIO JULIÀ ET AL: "An Eight-Gene Blood Expression Profile Predicts the Response to Infliximab in Rheumatoid Arthritis", PLOS ONE, vol. 4, no. 10, 1 January 2009 (2009-01-01), page e7556, XP055015104, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0007556	12,13
Y	the whole document	1,2,7-11

X	LEQUERRÉ THIERRY ET AL: "Gene profiling in white blood cells predicts infliximab responsiveness in rheumatoid arthritis", ARTHRITIS RESEARCH AND THERAPY, BIOMED CENTRAL, LONDON, GB, vol. 8, no. 4, 3 July 2006 (2006-07-03), page R105, XP021020585, ISSN: 1478-6354, DOI: 10.1186/AR1924	12,13
Y	the whole document tables 1,4	1,2,7-11

X	WO 2008/132176 A2 (UNIV LOUVAIN [BE]; CLINIQUES UNIVERSITAIRES SAINT [BE]; LAUWERYS BERNA) 6 November 2008 (2008-11-06)	12,13
Y	claims 1-32 the whole document	1,2,7-11

A	WO 2004/091657 A2 (GENENTECH INC [US]; BENYUNES MARK [US]) 28 October 2004 (2004-10-28) claims 1,2	1,2,7-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2013/000101

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 7-13(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 7-13(all partially)

Method for predicting whether a patient would be responsive to a treatment with a TNFa inhibitor, which method comprises determining the expression level of at least 6 genes selected from ABCC4, AIDA, ARHGEF12, BMP6, BTN3A2, CA2, CADM2, CD300E, CYP1B1, ENDOD1, FCGR1A, FMN1, GCLC, GPR34, HORMAD1, IGF2BP2, IL18R1, IL1RL1, KAT2B, MAP1LC3B, MMD, MS4A4A, MS4A7, ODC1, PBX1, PCYT1B, PIP4K2A, PIP5K1B, PRDM1, PSME4, RAD23A, RIOK3, RNASE2, RNF11, SLC7A5, THEM5, TMEM176A, TMEM176B, UBE2H, WARS genes in a biological sample of said patient, wherein one of the genes is ABCC4 . TNFa inhibitor for use in the treatment of a TNFa related disease, wherein the treated patient was classified as responder to a treatment with a TNFa inhibitor by the above method.

2-29. claims: 1, 2, 7-13(all partially)

Method for predicting whether a patient would be responsive to a treatment with a TNFa inhibitor as in invention 1, wherein one of the genes is the gene AIDA (BTN3A2, CA2, ENDOD1, FCGR1A, FMN1, GPR34, HORMAD1, IGF2BP2, IL18R1, IL1RL1, KAT2B, MAP1LC3B, MS4A4A, MS4A7, PBX1, PCYT1B, PIP4K2A, PIP5K1B, PRDM1, PSME4, RAD23A, RNASE2, SLC7A5, THEM5, TMEM176A, TMEM176B, WARS). TNFa inhibitor for use in the treatment of a TNFa related disease, wherein the treated patient was classified as responder to a treatment with a TNFa inhibitor by the above method.

30-40. claims: 1, 2, 5-13(all partially)

Method for predicting whether a patient would be responsive to a treatment with a TNFa inhibitor as in invention 1, wherein one of the genes is BMP6 (CD300E, CYP1B1, ODC1, RNF11, UBE2H, ARHGEF12, CADM2, GCLC, RIOK3, MMD). TNFa inhibitor for use in the treatment of a TNFa related disease, wherein the treated patient was classified as responder to a treatment with a TNFa inhibitor by the above method.

41. claims: 1, 2, 7-13(all partially)

Method for predicting whether a patient would be responsive to a treatment with a TNFa inhibitor, which method comprises determining the expression level of at least 6 genes selected from APOBEC3A, AQP9, CCL4, CNTNAP3, CYP4F3, DHRS9, EIF2AK2, ELOVL7, EPSTI1, FCGR3A, GPAM, GPR15, GZMB, IFI35, IFI44, IFI44L, IFI6, IFIT1, IFIT2, IFIT3, IFITM1, IL2RB,

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

IRF2, IRF7, MGAM, MICA, MME, MX1, OR2A9P, PF4, PTGS2, RAVR2, RFC1, RGS1, RSAD2, S100P, SERPINB10, SERPING1, SIGLEC1, TNF, TNFAIP6 genes in a biological sample of said patient, wherein one of the genes is AQP9 . TNFa inhibitor for use in the treatment of a TNFa related disease, wherein the treated patient was classified as responder to a treatment with a TNFa inhibitor by the above method.

42-67. claims: 1, 2, 7-13(all partially)

Method for predicting whether a patient would be responsive to a treatment with a TNFa inhibitor as in invention 41, wherein one of the genes is CCL4 (CNTNAP3, CYP4F3, EIF2AK2, EPSTI1, FCGR3A, GPAM, GPR15, GZMB, IFI6, IFIT2, IL2RB, IRF2, IRF7, MGAM, MME, MX1, PF4, PTGS2, RSAD2, S100P, SERPINB10, SERPING1, SIGLEC1, TNF, TNFAIP6). TNFa inhibitor for use in the treatment of a TNFa related disease, wherein the treated patient was classified as responder to a treatment with a TNFa inhibitor by the above method.

68-81. claims: 1-4, 7-13(all partially)

Method for predicting whether a patient would be responsive to a treatment with a TNFa inhibitor as in invention 41, wherein one of the genes is ELOVL7 (IFI44L, IFIT1, IFIT3, MICA, OR2A9P, RAVR2, APOBEC3A, IFI44, IFITM1, RGS1, DHRS9, IFI35, RFC1). TNFa inhibitor for use in the treatment of a TNFa related disease, wherein the treated patient was classified as responder to a treatment with a TNFa inhibitor by the above method.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/HU2013/000101

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1857559	A1	21-11-2007	AT 530670 T 15-11-2011
		CA 2652087 A1 29-11-2007	
		DK 2019872 T3 16-01-2012	
		EP 1857559 A1 21-11-2007	
		EP 2019872 A2 04-02-2009	
		ES 2375865 T3 07-03-2012	
		US 2009252740 A1 08-10-2009	
		WO 2007135568 A2 29-11-2007	

WO 2012061620	A1	10-05-2012	NONE

WO 2008132176	A2	06-11-2008	NONE

WO 2004091657	A2	28-10-2004	AT 425766 T 15-04-2009
		AU 2004229376 A1 28-10-2004	
		BR PI0409534 A 18-04-2006	
		CA 2519870 A1 28-10-2004	
		CN 1802176 A 12-07-2006	
		CN 101371924 A 25-02-2009	
		CR 8033 A 18-08-2006	
		DK 1613350 T3 22-06-2009	
		EC SP056082 A 19-04-2006	
		EP 1613350 A2 11-01-2006	
		EP 2062916 A2 27-05-2009	
		ES 2322267 T3 18-06-2009	
		HK 1086480 A1 07-08-2009	
		HR P20050940 A2 31-12-2005	
		HR P20090325 T1 31-07-2009	
		IL 171038 A 30-06-2010	
		IL 203019 A 29-02-2012	
		JP 2006522811 A 05-10-2006	
		JP 2010047586 A 04-03-2010	
		JP 2013151515 A 08-08-2013	
		KR 20050114273 A 05-12-2005	
		KR 20110044809 A 29-04-2011	
		MA 27838 A1 03-04-2006	
		MX PA05010778 A 12-12-2005	
		NZ 580116 A 30-06-2011	
		NZ 587776 A 30-03-2012	
		PT 1613350 E 24-06-2009	
		RS 51686 B 31-10-2011	
		RS 20050761 A 15-11-2007	
		RU 2358762 C2 20-06-2009	
		SI 1613350 T1 31-08-2009	
		US 2004202658 A1 14-10-2004	
		US 2006240008 A1 26-10-2006	
		US 2008213280 A1 04-09-2008	
		US 2011300136 A1 08-12-2011	
		WO 2004091657 A2 28-10-2004	
		ZA 200507805 A 27-12-2006	
